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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
08/465,596	06/05/1995	RICHARD F. SELDEN	9515	2132

7590 07/27/2005

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EXAMINER	
CROUCH, DEBORAH	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 07/27/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	08/465,596	SELDEN, RICHARD F.	
	Examiner	Art Unit	
	Deborah Crouch, Ph.D.	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *72-78,82-84 and 104-108* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *72-78,82-84 and 104-108* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *6/5/95* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Claims 72-78, 82-84 and 104-108 are pending. The terminal disclaimers filed April 18, 2005 have been approved.

Applicant is advised that formal drawings have not been received. Applicant should refer to the PTO-948 mailed April 29, 1996.

In review of the claims, it was decided the following rejections are proper and should be instated against the claims. As these are new rejections, this office action is non-final.

Claims 72-78, 82-84 and 104-108 are rejected over the count, claim 36 of 08/465,582, lost in Interference No. 104714. Applicant requested adverse judgment.

The count is repeated here:

36. A process for providing a human with a therapeutic protein comprising:

introducing human cells into a human, said human cells having been treated in vitro to insert therein a DNA segment encoding a therapeutic protein said human cells expressing in vivo in said human a therapeutically effective amount of said therapeutic protein.

As the count encompasses all the limitations disclosed in the specification, the limitations of the present claims are inherently found in the above count.

Further, applicant is estopped from prosecution of the present claims. 37 CFR 1.658(c) states:

> A losing party who could have properly moved, but failed to move, under § 1.633 or 1.634, shall be estopped to take ex parte or inter partes action in the Patent and Trademark Office after the interference which is inconsistent with that party 's failure to properly move, except that a losing party shall not be estopped with respect to any claims which correspond, or properly could have corresponded, to a count as to which that party was awarded a favorable judgment.

Applicant did not move to have the present claims added into Interference No. 104714, and could have since applicant's use of the term "cloning" only is taken to mean those cells selected and then expanded. The specification does not disclose

more treatment of the cells than selecting, which produces clones that are antibiotic resistant, and expanding those cells. Thus, applicant is estopped.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 72-78, 82-84 and 104-108 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The limitation in claims 72 and 104 "wherein, following injection of the transfected, screened, cloned, and expanded somatic cells into the recipient subject, the DNA sequence is incapable of recombining with endogenous retroviral sequences, and the DNA sequence is incapable of initiating chronic viral infection in the recipient subject" is not described in the specification to convey to one skilled in the art at the time of filing that application had possession of the presently claimed invention.

In the amendment filed October 5, 1999, where this amendment to the claims appeared in its original form, applicant cited support in the specification, page 40, lines 7-9; page 44, lines 21-22; page 4, line 16 through page 5, line 4; and page 6, lines 27-31. A review of these citations fails to provide such support. At page 40, lines 7-9, the specification discloses a plasmid, at page 44, lines 21-22, the specification discloses the specific promoter used in the plasmid of the specific example, at page 4, line 16 through page 5, line 4, several issues are described concerning retroviral use as gene delivery vectors in gene therapy methods, and page 6, lines 27-31, describes the potential problem

of endogenous gene rearrangement and potential of inducing cancer formation. However, at none of these citations is there a description of the DNA sequence transfected into the cell as being incapable of causing recombination of the DNA sequence with endogenous retroviral sequences. The disclosure of art-recognized problems does not convey anything specific about the structure of the DNA sequence transfected into the cells. Further, the problems discussed with retroviral vectors or with endogenous gene rearrangement all are directed to in vivo gene therapy, not applicant's invention of ex vivo gene therapy. Thus, there is no clear evidence from these art-recognized problems with retroviruses and in vivo gene therapy methods that applicant possessed the claimed invention at the time of filing. The specific description of a plasmid furthermore does not convey to skilled artisan at the time of filing the genus of DNA sequences, although it would convey the species "plasmid."

Claims 72-78, 82-84 and 104-108 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Present claims 72-78, 82-84 and 104-108 are drawn to a method of transferring a agene into a recipient subject comprising transfecting somatic cells in vitro with a DNA sequence comprising a gene, screening the resulting transfected cells, cloning and expanding the selected somatic cells in vitro and injecting the resulting transfected, screened, cloned and expanded somatic cells into a recipient subject wherein the DNA sequence comprises the gene and a promoter, wherein, following injection of the transfected, screened, cloned, and expanded somatic cells into the recipient subject, the DNA sequence is incapable of recombining with endogenous retroviral sequences, and the DNA sequence is incapable of initiating chronic viral infection in the recipient subject, where the

gene encodes a hormone, an enzyme or a receptor, and where the somatic cells are endothelial cells, fibroblasts, myocytes, heptatocytes and other cell types.

It is noted that in a parallel interference (I104712), the Board of Interferences found that methods of gene therapy by implantation of transformed cells were not enabled except for a narrow scope to one party. Thus, there are no apparent differences between the present claims and those in interference 104712, the present claims likewise must lack enablement. The rejection below is based upon reasoning set forth the '712 judgment, and expanded.

Lindahl (1990) states that normal, transduced cells, as compared to established cell lines, do not have the ability to express a heterologous protein and have it appear in the serum (page 398, lines 1-3). Lindahl further indicates that there is promoter variability in epithelial cells (page 398, parag. 1, line 2-5). Mulligan (1993) states, with regard to *ex vivo* gene therapy, as presently claimed, that transduced and transplanted keratinocytes, a type of epithelial cell, have shown some low level of gene expression, but a vector-encoded gene product has not been sufficiently delivered to the circulation for sustained periods of time while endogenous gene products are efficiently delivered to the circulation (page 930, col. 1, lines 1-7). Mulligan further states that the transplantation of transduced cells remains the most serious technical obstacle to successful *ex vivo* gene therapy (page 931, col. 1, parag. 1, lines 1-4).

Greenhalgh (1994) states, with regard to retroviral transduction of epithelial cells, that it is difficult to predict the influence of host cell genomic sequences surrounding the integration site of the retrovirus on expression of the therapeutic gene (page 65S, col. 1, parag. 1, lines 8-10). Greenhalgh also states that other viruses such as AAV could be used, but that they are less well developed in gene therapy protocols (page 65S, col. 1, parag. 1, lines 15-17). Ghazizadeh (2000) states that a perplexing issued with *ex vivo* gene therapy is the loss of expression which cultured, transduced keratinocytes are transplanted (page 2248, col. 2, parag. 2, parag. 2, line 1-5). This problem was thought to be due to methylation of the retrovirus promoter, but the addition of other promoters to the virus did not overcome the problem of

inadequate expression (page 2248-2249, bridg, sent.). Thus, the art establishes that at the effective time of filing, May 1, 1987, the art did not expect that *ex vivo* gene therapy by transplanting transduced epithelial would have resulted in a therapeutic effect. Further, there is no reason to believe that these problems with ex vivo gene therapy would not have been present in any transformed cell at the time of filing.

The specification discloses the implantation of cells expressing human growth hormone or human insulin. Human growth hormone could only be found in the serum of implanted mice only as long as there were viable transformed cells (specification, page 45, parag. 1). Further, mice implanted intraperitoneally with transformed cells producing human growth hormone died (specification, page 49, parag. 1). Mice implanted with cells producing human insulin died from transkaryotic implantation-induced hypoglycemia (specification, page 52, lines 27-30). Thus, the specification is not enabling for the method of transferring because, not only was a therapeutic effect not observed, the mice of the two specific examples died. The specification does not provide guidance for the method without resultant death of the mice implanted. It is noted that the only use for the presently claim method of transferring a gene is to obtain a therapeutic effect (specification, page 2, parag. 3; page 5, parag. 1; and page 21, III, as examples).

Thus, at the time of filing, the skilled artisan would have needed to engage in an undue amount of experimentation without a predictable degree of success to make and use the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 72-78, 82-84 and 104-108 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 72 states in step (a) "transfecting somatic cells in vitro with the DNA sequence... ." However, there is no antecedent basis in claim 72 for "the DNA sequence" in step "a." Applicant should amend step "a" to "a DNA sequence." Further, claims 72 states "wherein the DNA sequence comprises the gene .." It is improper to refer to the preamble for antecedent bases. Applicant should amend the claims to state "wherein the DNA sequence comprises a gene."

Claim 104 (b) states "a DNA sequence comprising the gene .." It is improper to refer to the preamble for antecedent bases. Applicant should amend the claims to state "a DNA sequence comprises a gene."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is 571-272-0727. The examiner can normally be reached on M-Th, 8:30 AM to 7:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla, Ph.D. can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Deborah Crouch

Deborah Crouch, Ph.D.
Primary Examiner
Art Unit 1632

July 9, 2005